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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,001	11/03/2005	Tetsu Akiyama	3190-078	7470

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KILYK & BOWERSOX, P.L.L.C.
400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/537,001	AKIYAMA ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-51* is/are pending in the application.

4a) Of the above claim(s) *27-32,35,36,39-41 and 43-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,33,34,37,38 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-11-05 & 11-2-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments/Election/Restrictions

Applicant's election with traverse of claims 26, 33-34, 37-38 and 42 pertaining to an agent for inhibiting metastasis of colorectal cancer that inhibits Asef expression, in the reply filed on July 14, 2006 is acknowledged. The traversal is on the ground(s) that 1) there is no serious burden on the examiner to search the entire scope of the claims, that 2) the International Search Authority found a single inventive concept, 3) and that the cited prior art by the examiner does not establish the lack of unity of the claimed invention. This is not found persuasive because of the reasons stated below:

1) The presence or absence of "serious burden" was not at all argued or stated in the Office action for election/restrictions mailed to the applicant on May 16, 2006. Further, search "burden" is not a factor for determining the presence of absence of unity of invention in applications that enter national stage under 35 U.S.C 371 and 37 CFR 1.495, which is the case with the instant application.

2) Applicant argues that the International Search Authority found a single inventive concept by examining all claims. Contrary to applicant's assertions, the different inventions of the instant application, according to domestic (U.S.) restriction practice, comprise functionally, chemically, and biologically distinct compositions and methods, and thus comprise patentably distinct inventions.

3) Applicant argues that the examiner cited a reference not included in the IDS and that its copy was not provided, which required of the applicant to obtain a "partial English

translation". This is found confusing because it is the examiner's understanding that the examiner is not restricted to use the references listed only in the IDS, thus can rely on any pertinent prior art. Applicant is encouraged to cite the proper statute or rule that states that the examiner is bound to rely only on the references disclosed in the applicant's IDS. Applicant's allegation that a "partial English translation" was required for the examiner's cited reference, Senda et al., is found unsubstantial and irrelevant because not only is the entire reference available on the World Wide Web at no charge, for example, via PubMed, but also the entire Senda et al. document is written in English. See the Senda et al. citation (reference No. U, Form PTO-892).

4) In response to applicant's argument that the combined references cited by the examiner do not "effect the general inventive concept of the claimed invention", the examiner hereby reiterates the teachings of each reference as following: Senda et al. explicitly teach that APC gene is involved in development of colorectal carcinomas (page 329) and clearly state the significance of identifying novel APC-associated proteins (page 333); Kawasaki et al. expressly teach that APC and Asef colocalize in colon epithelial cells and that APC and Asef interact with each other *in vivo*. In view of the *in vivo* biological interaction between APC and Asef, their co-expression in colon cells, and the fact that APC is implicated in causing colorectal cancer, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time of the instantly claimed invention, to make an agent that inhibits Asef expression, thereby inhibiting colorectal cancer metastasis. Accordingly, the claimed invention of claim 1, as originally filed, does not contribute over the combined teachings of the prior art, thus the unity of invention is lacking.

The requirement is still deemed proper and is therefore made FINAL.

Pending Claims

Claims 1-25 have been cancelled. Claims 26-51 are pending. Claims 27-32, 35-36, 39-41, and 43-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Accordingly, claims 26, 33-34, 37-38 and 42 pertaining to Asef gene and SEQ ID NO:1 are currently under examination.

Claim Objections

Claim 38 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. As claimed, the subject matter of claim 38 does not constitute a further limitation of a previous claim, claim 37, because an oligonucleotide having SEQ ID NO:1 set forth in claim 37 is same as an agent for inhibiting Asef, wherein the agent comprise an oligonucleotide having SEQ ID NO:1 as set forth in claim 38. The oligonucleotide having SEQ ID NO:1 of claim 37 is targeted to the Asef gene sequence, thus it will inherently function as an agent for inhibiting Asef as claimed in claim 38.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 26 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and /or chemical properties, functional characteristics, structure/function correlation, or any combination thereof.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), which clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (see page 1117). As broadly claimed, the term "agent" in claim 26 reads on any agent that inhibits the expression of the Asef gene such as an antibody, a peptide, a small molecule, an siRNA, an antisense, a ribozyme, a DNAzyme, and so forth. Although the instant specification provides "Asef-ABR dominant negative mutant" (Examples 6-7) and "shRNA-Asef" (paragraph 0103) as agents that inhibit the expression of the Asef gene, it does not provide any other inhibitory agents that inhibit the expression of the Asef gene. Since the instant specification lacks disclosure of complete or partial structure, physical and /or chemical properties, functional characteristics, structure/function correlation, or any combination thereof with regard to the broad genus of

"agent", one of ordinary skill in the art cannot recognize what is claimed in claim 26 or whether the inventor was in possession of the presently claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 26 and 33-34 are rejected under 35 U.S.C. 102(a) as being anticipated by Jimbo et al. (*Molecular Medicine,* 2002, also applicant's citation submitted in the form 1449A/PTO, filed August 11, 2005).

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. However, applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claims 26 and 33-34 are drawn to an agent for inhibiting metastasis of colorectal cancer, wherein the agent inhibits the expression of the Asef gene (claim 26) by the RNA interference (claim 33) and said agent comprises an oligonucleotide that exhibits an RNA interference effect on the expression of Asef (claim 34).

Jimbo et al. disclose on page 1278 that expression of Asef is decreased in colorectal cancer cell lines via RNAi mechanism, indicating a sequence-specific double-stranded RNA molecule targeted against Asef must have been transfected into the colorectal cancer cell lines. Accordingly, all the limitations of instantly claimed invention are met by Jimbo et al.

Claims 26 and 33-34 are rejected under 35 U.S.C. 102(a) as being anticipated by Akiyama (*Journal of Clinical and Experimental Medicine*, 2003, also applicant's citation submitted in the form 1449A/PTO, filed August 11, 2005).

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. However, applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Akiyama discloses that RNAi against Asef causes marked inhibition of cell motility in colorectal cancer cell line, indicating the role of RNAi against Asef in inhibiting colorectal cancer metastasis, thus meeting all the limitations of instantly claimed invention.

Claims 26, 37-38, and 42 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Drmanac et al. (US 2003/0073623 A1).

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. However, applicant cannot rely upon the foreign priority papers to overcome the 102(a) rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. Applicant is reminded that the

102(e) rejection will remain valid even if a translation of said papers are submitted because the reference of Drmanac et al. has an earlier effective date than the instant application.

Claims 26, 37-38, and 42 are drawn to an oligonucleotide/agent having the nucleotide sequence set forth in SEQ ID NO:1 for inhibiting metastasis of colorectal cancer, wherein the oligonucleotide/agent inhibits the expression of the Asef gene.

Transitional phrases such as "having" must be interpreted in light of the specification to determine whether open or closed claim language is intended. See, e.g., *Lampi Corp. v. American Power Products Inc.*, 228 F.3d 1365, 1376, 56 USPQ2d 1445, 1453 (Fed. Cir. 2000), in which the term "having" was interpreted as open terminology, allowing the inclusion of other components in addition to those recited. See MPEP §2111.

The instant specification expressly discloses that "the expression of the Asef gene can be inhibited by using an oligonucleotide that exhibits an RNA interference effect on the expression of the Asef gene. Examples of the oligonucleotide can include a cDNA having the nucleotide sequence set forth in SEQ ID NO:1 in the sequence listing (paragraph 0049, page10). Thus, the transitional term "having" recited in claims 37-38 and 42 is synonymous with "including," "containing," or "characterized by," which is inclusive or open-ended and does not exclude additional, unrecited elements. See , e.g., *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997), in which the Court stated: "Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim". See also *Ex parte Davis*, 80 USPQ 448, 450 (Bd.App. 1948), which stated that "comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts".

In view of the foregoing, an oligonucleotide containing the instant SEQ ID NO:1 constitutes the instantly claimed invention. Drmanac et al. disclose an isolated polynucleotide identified as SEQ ID NO: 1044, wherein nucleotides 152 to 182 of said SEQ ID NO:1044 perfectly correspond to the full length of the instant SEQ ID NO:1. They further disclose that SEQ ID NO:1044 can be used in generation of antisense DNA or RNA (paragraph 0012). They disclose that the fragments of SEQ ID NO:1044 can be used to control gene expression through triple helix formation or antisense DNA or RNA that binds to an mRNA sequence thereby blocking translation of the mRNA molecule (paragraph 0162-0163). Moreover, They disclose that the agents suitable for control of gene expression usually contain 20 to 40 bases and are designed to be complementary to a region of the target gene (paragraph 0183).

Since Drmanac et al. teach the essential ingredient of the claimed invention that meets the structural limitations of claims 26, 37-38, and 42, the instantly claimed invention is clearly anticipated by the disclosure of Drmanac et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 26, 33-34, 37-38 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawasaki et al as applied to claim 26 for §103 rejection above, further in view of Fire et al. (US 6,506,559 B1) and Costa et al. (US 2003/0157531 A1).

Claims 26, 33-34, 37-38 and 42 are drawn to an agent that inhibits expression of the Asef gene (claim 26), wherein the agent inhibits the Asef gene expression via the RNA interference (claims 33-34), and an oligonucleotide having SEQ ID NO:1 (claims 37-38 and 42).

Kawasaki et al. teach the full length nucleic acid sequence of Asef, which has been deposited in GenBank with an accession number AB042199. See the legend for Figure 1 (B) on page 1195. The instant SEQ ID NO:1 corresponds to the nucleotides 905 to 935 of the GenBank accession number AB042199. They also teach that both APC and Asef are expressed in mouse colon epithelial cells and that APC gene is mutated in colorectal cancer patients (pages 1194-1195). Further, they teach that APC gene interacts with β-catenin and that Asef, APC, and β-catenin are contained in the same complex *in vivo* (pages 1194-1195). Kawasaki et al. do not teach an oligonucleotide having the GenBank accession number AB042199, which is capable of inhibiting the Asef gene expression via RNAi.

However, it was routine in the art, at the time the instantly claimed invention was made, to make an oligonucleotide against a known target gene sequence in order to inhibit the gene expression via RNAi, particularly to inhibit tumor cell metastasis.

Fire et al. teach that short interfering double-stranded RNA molecules mediate sequence-specific inhibition of gene expression, which is known as RNA interference (RNAi) phenomenon (columns 3-6 and column 14, lines 52-53). They further teach that the double-stranded RNA molecules may be introduced into a cancerous cell or tumor of any type including colorectal neoplasmic carcinoma, and thereby inhibit the expression of a gene required for maintenance of the carcinogenic/tumorigenic phenotype (column 9, lines 65-67; column 10, lines 1-2, 26-30, and 67; and column 11, line 1).

Furthermore, making an siRNA molecule that inhibits the expression of a gene implicated in colorectal cancer metastasis via RNAi was also routine in the art at the time the instantly claimed invention was made. For instance, Costa et al. teach that a double-stranded RNA that is homologous in sequence to the target gene, TAO/JNK kinases, can be used to inhibit the activity of the β-catenin signaling pathway that is implicated in colorectal cancer metastasis (paragraphs 0002, 0005, 0011, and 0065). Moreover, they teach that siRNA oligonucleotides targeting TAO/JIN kinases inhibit cell proliferation in colon cancer cell lines (paragraphs 0157-0163).

It would have been obvious to one of ordinary skill in the art, at the time the instantly claimed invention was made, to make an siRNA oligonucleotide targeting the Asef gene sequence in order to inhibit the expression of the Asef gene *in vitro*. One of ordinary skill in the art would have been sufficiently motivated to inhibit the expression of Asef by targeting its

cDNA sequence of Kawasaki et al. since it was an art-recognized goal to inhibit the expression of a gene implicated in colorectal cancer metastasis *in vitro* as taught by Costa et al. and since Kawasaki et al. explicitly teach that Asef is expressed in colorectal epithelial cells and interacts with APC (a gene mutated in colorectal cancer as taught by Kawasaki et al., pages 1194-1195). Further, the skilled artisan would have been motivated to make an siRNA oligonucleotide of Fire et al. and Costa et al. in order to inhibit the expression of Asef in colorectal cancer cells thereby inhibiting colorectal cancer metastatic cells *in vitro* with a reasonable expectation of success, because the siRNA oligonucleotide of Costa et al. effectively inhibited cell proliferation in colon cancer cell lines by inhibiting the biochemical signaling activity of the Asef-interacting gene, β-catenin, at the time the instantly claimed invention was made and because Fire et al. expressly teach that siRNA molecules can be used to inhibit gene expression that is implicated in colorectal neoplasmic carcinoma. Accordingly, the claimed invention, taken as a whole, is *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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TC1600

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